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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,293	03/16/2005	Cangyou Zhou	21055P	6442

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,293	ZHOU ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *41-53,55 and 56* is/are allowed.

6)☒ Claim(s) *57-59* is/are rejected.

7)☒ Claim(s) *54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/US03/33980 filed 10/24/2003 which claims benefit of 60/422,355 filed 10/30/2002.

Claims 41-59 are pending.

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 14, 2009 has been entered.

Claim Rejections/Objections Withdrawn

3. The objections/rejections of claims are withdrawn. The amendments submitted obviate the rejections for new matter, as well as the scope enablement rejections.

New Objections/Objections maintained

4. The objection to the specification for a misspelling is maintained. A minor objection to claim 54 is raised.

Rejoinder

5. Claims 41-53, 55 are allowable. Claim 54 is objected to for a minor error. Claims 56-59, previously withdrawn from consideration as a result of a restriction requirement, November 16, 2007 requires all the limitations of an allowable claim. Pursuant to the procedures set forth in

MPEP § 821.04(a), **the restriction requirement between inventions IV and XII, as set forth in the Office action mailed on November 16, 2007 is hereby withdrawn** and claims 56-59 hereby rejoined and fully examined for patentability under 37 CFR 1.104. In view of the withdrawal of the restriction requirement, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Objections

Specification

5. The spelling of "dedydroproline", on page 51 and other pages is probably meant to be dehydroproline

Appropriate correction is required.

Claims

6. Claim 54 is objected to because of the following informalities: Claim 54 references "formula I and II below", however formula II was canceled from the claim. The examiner believes that this was a minor oversight. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 57-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing any "inflammatory or immunoregulatory disorder or disease" with a variety of compounds. According to the specification such diseases include, but are not limited to:

inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilie pneumonia), delayed-type hypersentitivity, interstitial lung diseases OLD) (e.g., idiopathie pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes; glomemlonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease;

inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such an dermatitis, eczema, atopie dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilie fasciitis; cancers with leukocyte infdtration of the skin or organs, reperfusion injury, atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis, immunosuppression, such as that in individuals with immunodefieiency syndromes such as AIDS or other viral infections, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or drug therapy (e.g., eorticosteroid therapy), which causes immunosuppression; immunosuppression due to congenital deficiency in receptor function or other causes; and infections diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms), (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis, filariasis), trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinocoecosis, Taeniasis saginata, Cysticercosis), visceral worms, visceral larva migraines (e.g., Toxocara), eosinophilic gastroenteritis (e.g., Anisaki sp., Phocanema sp.), and cutaneous larva migraines (Ancylostona braziliense, Ancylostoma caninum), rheumatoid arthritis or psoriatic arthritis, infection by a retrovims, in particular, herpes virus or the human immunodeficiency virus (HIV).

(B) The nature of the invention: This is a medical invention requiring the treatment of a complex disease states with compounds.

(D) The level of one of ordinary skill: One of ordinary skill is a medical doctor.

(C) The state of the prior art, (E) The level of predictability in the art, (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention.

The claims are drawn to methods treating diseases. The only information provided in the specification as to what the compounds may be doing, at least in the pharmacological sense, is on pg. 24 -25 of the disclosure (reproduced here):

" The present invention is directed to the use of the foregoing compounds as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, in particular CCR-2.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for chemokine binding as disclosed by Van Riper, et al., J. Exp. Med., 177, 851-856 (1993) which may be readily adapted for measurement of CCR-2 binding.

Receptor affinity in a CCR-2 binding assay was determined by measuring inhibition of 125I-MCP-1 to the endogenous CCR-2 receptor on various cell types including monocytes, THP-1 cells, or after heterologous expression of the cloned receptor in eukaryotic cells.....the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an IC50 of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity."

This is a reference to receptor binding data for the CCR2 receptor. While the last paragraph states that these compounds bind, no specific data for any particular compounds is listed in the specification. Nonetheless, it is unclear what these compounds are doing other than binding the receptor. A plethora of compounds bind CCR2 receptors including CCL7, CCL8, CCL13, CCLl6. The complexity and the functional redundancy of the chemokine system means that while one ligand or receptor may be disrupted the system will continue to function. Each chemokine receptor has unique binding sites, physiological effects, etc. The number of coupling partners associated with this GPCR is quite large, the interaction with these proteins and the subsequent signaling is poorly understood. Medical interest centers on antagonism of chemokine receptors. The most basic functional characterization of these compounds as agonists, partial agonists, or antagonists has not been conducted. Presumably to treat inflammatory diseases, one would need to antagonize an endogenous ligand, and not stimulate the receptor. The experimental data given does not support antagonism, as only binding data is presented. Assuming *arguendo* that the compounds were in fact antagonists of all known CCR2 ligands and essentially blockaded all CCR2 receptor function, there is only a very small group of the diseases that might be treatable. A compound that would treat all the conditions listed above is contrary to

our present understanding of pharmacology and medicine. No such magic bullet exists. Moreover, data from CCR2 null mice show that for rheumatoid arthritis (the narrowest embodiment of claim 59) the condition still occurs. The causal link between CCR2 and rheumatoid arthritis is not strong. For a detailed analysis see Quinones et.al. "The complex role of the chemokine receptor CCR2 in collagen-induced arthritis: implications for therapeutic targeting of CCR2 in rheumatoid arthritis" Journal of Molecular Medicine **2005** *83*: 672–681,

"Despite the well-documented role of CCR2 in regulating the induced trafficking of macrophages, it was surprising to find that the diseased joints of CCR2-null mice contained a high proportion of macrophages, as measured both by FACS analysis of the cells isolated from inflamed joints and by RNase protection assays to measure transcript levels of the macrophage cell surface markers F4/80[33, 36]. The inflamed joints of WT mice treated with anti-CCR2 antibodies in the progressive stages of CIA also showed a significant increase in macrophages, interestingly all of which are CCR2+. Such CCR2-independent macrophage recruitment has also been demonstrated in other experimental systems [37, 38]. **Thus, in all of these cases there does not appear to be a direct correlation between CCR2 expression and macrophage accumulation, a cornerstone of the anti-CCR2 therapeutic rationale, suggesting that alternative mechanisms are in place to lure macrophages (and other cell types) to inflamed joints, in the absence of CCR2 signaling.**" pg. 674

In the conclusion the authors state:

"**The data review this far demonstrate that it is too premature to draw final conclusions regarding the role of CCR2 and CCR5 in RA.** This is in part because the implicit complexity of the chemokine system. The system has three major properties [67]. First, chemokines are redundant in their action on target cells, implying that so far there is no data demonstrating that a chemokine is uniquely active on any one particular leukocyte population. In general a given leukocyte population has receptors for, and responds to, different chemokines. Interestingly, mononuclear phagocytes, one of the most evolutionary ancient cell type involved in innate immunity, respond to the widest range of chemokines. Second, the interaction of chemokines with their receptors is characterized by considerable promiscuity. Most known receptors have been reported to interact with multiple ligands and most ligands interact with more than one receptor. For instance, all four monocyte chemotactic proteins (MCPs) interact with CCR2, and at least MCP-2, MCP-3 and MCP-4 also recognize other receptors (CCR1 and CCR3); indeed, because of this promiscuity, we have found that after exposure to the same challenge and under identical laboratory conditions, CCR2 and MCP-1 null mice (same genetic background i.e., C57BL/6), exhibit different outcomes (Ahuja et al., unpublished data). Third, multiple chemokines are produced in a redundant way by a single cell (polyspeirism)."

This receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore**, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation**..... "

Here we have exactly this situation, namely a ligand with affinity, but limited information about its function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." It is not possible to predict *a priori* how the pharmacological data as shown would translate into treatment efficacy in the complex diseases listed above. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). A medical doctor or Pharm. D. would not use these compounds to treat patients. Given the mechanism that applicant alleges and the current knowledge in the art, we cannot think that these compounds have a use in therapy. As Per MPEP:

CORRELATION: IN VITRO /IN VIVO
The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

The factors outlined in *In Re Wands* mentioned above apply here. It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the

organization where this application or proceeding is assigned is 571-273-8300.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David K. O'Dell/

Examiner, Art Unit 1625